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ALLEN, M

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on preliminary amendment 6/23/93 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1, 6-10, 12-15 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☑ Claims 2-5, 11 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1, 6-10, 12-15 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☑ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☑ been filed in parent application, serial no. 07/369686 ; filed on 6/21/89.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Claims 2-5 and 11 have been canceled previously.

Claims 6-9, drawn to a process for the preparation of mini-proinsulin compounds, DNA sequences, plasmids, and host cells, were restricted from original claims 1-5 and 10 in Paper No. 7. Applicant introduced new claims 11-15 during prosecution of the parent application. Claims 14-15 recite limitations to recombinant production using DNA sequences and host cells. These claims could have been properly grouped with claims 6-9 according to the initial restriction requirement and withdrawn from further consideration. However, these claims were examined on the merits in the parent application and as such, groups I and II of the original restriction requirement are hereby rejoined.

Claims 1, 6-10, and 12-15 have been examined on the merits.

The amendment after final rejection has been entered and the arguments therein considered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim 6 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 17 of U.S. Patent No. 5,227,293. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 6 of the instant application is drawn to production of any fusion protein of mini-proinsulin followed by cleavage. Claim 17 is drawn to a method of producing a specific fusion protein of mini-proinsulin with a cleavable site. (See examples 16 and 17 of U.S. Patent No. 5,227,293 which exemplify the proinsulin of the claims wherein the C chain is arginine.) While the method of claim 17 does not include a step of cleavage, it would have been obvious to cleave the fusion protein of claim 17 to produce the desired mini-proinsulin precursor as in claim 6. One would have been motivated to do so as this is a routine step when using fusion protein techniques.

It is noted that U.S. Patent No. 5,227,293 is not prior art against the instant application under 102(e)/103.

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. In re Vogel, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or

patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d).

Claims 1 and 6-9 are rejected under 35 U.S.C. § 103 as being unpatentable over either Markussen et al. (U.S. Patent No. 4,916,212) or Markussen et al. (EPO 163,529).

Markussen et al. ('212) discloses and claims insulin precursors of the form B(1-29)-X_n-Y-A(1-21). "X" is a peptide chain with n amino acids, "n" is an integer from 0 to 33, and "Y" is Lys or Arg. X is preferably selected from the group consisting of Ala, Ser, and Thr. A preferred embodiment is B(1-29)-Ser-Lys-A(1-21). This precursor protein is a single peptide chain. This precursor is converted to human insulin by derivatization and treatment with trypsin. (See '212 at column 2, line 65, through column 3, line 46; Examples 11, 13, and 16; and claims.) Fusion proteins and their cleavage from the precursor are disclosed. (See column 5, lines 11-20.) DNA sequences encoding the insulin precursor, expression vectors, transformed yeast cells, and recombinant methods of production in yeast are also disclosed and claimed.

Markussen et al. ('529) teaches essentially the same invention. (See pages 5-6, 8; Table 1; Example 11, page 26; Example 13, page 29; Example 16, page 30; claims.)

Claim 1 is drawn to a human insulin variant that is a single peptide chain of the formula B(1-30)-Arg-A(1-21). The amino acid

at position 30 in native human insulin is Thr. This position is equivalent to the "X" of Markussen et al.

Markussen et al. suggests the claimed mini-proinsulin precursor, DNA sequences encoding it, vectors, host cells and process for preparation where "X" is Thr, "n" is 1, and "Y" is Arg. This is a very similar structure to the preferred embodiment B(1-29)-Ser-Lys-A(1-21). The claimed generic formula of the prior art encompasses applicant's claimed composition. The different amino acids selected by applicant for these positions are preferred embodiments in the prior art.

Claim 6 is rejected under 35 U.S.C. § 103 as being unpatentable over Markussen et al. (EPO 163,529) or Markussen et al. (U.S. Patent No. 4,946,828) either in view of Goeddel et al. (EPO 055,945).

Both Markussen et al. references are applied as above.

Goeddel et al. teaches producing recombinant fusion proteins of insulin precursors fused to another protein and cleaving them. The reference further teaches making a fusion protein with an insulin variant in which the C chain of insulin contains only six amino acids. (See page 6, line 19 through page 8, line 2; abstract; claims; pages 26-27.)

It would have been obvious to make fusion proteins as taught by Goeddel et al. using the insulin precursor, DNA sequences, and

vectors taught by either Markussen et al. reference. It would have been further obvious to cleave the fusion protein to release the desired protein as taught by Goeddel et al. One would have been motivated by the known benefits of producing small peptides as fusion proteins in bacterial and yeast hosts and the success with another insulin variant in which the C chain is shortened. The usefulness of fusion proteins is suggested by Markussen et al.

Claim 10 is rejected under 35 U.S.C. § 103 as being unpatentable over Markussen et al. (EPO 163,529) or Markussen et al. (U.S. Patent No. 4,946,828) either in view of Goeddel et al. (EPO 055,945) and Mai et al. (U.S. Patent No. 5,087,564).

Both of the Markussen et al. references and Goeddel et al. are applied as above.

Mai et al. teaches that it would have been well known in the art to use common cleavage sites in fusion proteins. The reference teaches that cyanogen bromide cleaves after the amino acid Met and that factor Xa cleaves after the tetrapeptide Ile-Glu-Gly-Arg. (See column 3, line 14, through column 4, line 35, especially column 3, line 67, through column 4, line 1; and column 9, lines 7-19.)

It would have been obvious make the miniproinsulin of Markussen et al. as a fusion protein using the cleavable sequence Met-Ile-Glu-Gly-Arg. Markussen et al. suggests making fusion

proteins that can be cleaved as does Goeddel et al. The recited sequence includes cleavage sites for cyanogen bromide and factor Xa that would have been commonly used in fusion proteins. One would have been motivated to make a fusion protein for the reasons taught by Markussen et al., Goeddel et al., and Mai et al.

Claims 12-13 and 15 are rejected under 35 U.S.C. § 103 as being unpatentable over Markussen et al. (EPO 163,529) or Markussen et al. (U.S. Patent No. 4,946,828) either in view of Grau (U.S. Patent No. 4,801,684) and Grau (U.S. Patent No. 4,639,332).

Both Markussen et al. references are applied as above.

Grau ('684) teaches using trypsin and carboxypeptidase B simultaneously to produce mature insulin from proinsulin. (See column 5, lines 49-59.)

Grau ('332) teaches that treatment of proinsulin with trypsin alone gives intermediates with an arginine at B31. This insulin-Arg^{B31}-OH derivative is stable to further tryptic degradation. Enzymes having both tryptic and carboxypeptidase B are required to produce insulin. (See column 1, lines 1-32; column 2, lines 10-12.)

The intermediate disclosed by Grau ('332) is the mono-Arg insulin of claim 12 and formula II of claim 15.

With respect to claims 12 and 13, it would have been obvious

to use both trypsin and carboxypeptidase B to convert the miniproinsulin of Markussen et al. first to Mono-Arg insulin and then to insulin. Grau ('332) teaches that Mono-Arg insulin can be formed by trypsin cleavage and that this form is resistant to further tryptic degradation and Grau ('684) teaches that the combination of trypsin and carboxypeptidase B together can convert proinsulin to insulin. One would have been motivated to use both trypsin and carboxypeptidase B in order to produce insulin from the precursor of Markussen et al. for treating diabetes.

With respect to claim 15, it would have been obvious to prepare Mono-Arg insulin by expressing a DNA molecule encoding miniproinsulin in yeast as taught by Markussen et al. and cleaving this compound with trypsin as taught by Grau ('332 and '684) to produce Mono-Arg insulin. One would have been motivated to produce a stable intermediate of insulin for further treatment with carboxypeptidase B to produce insulin for treating diabetes.

Claim 14 is rejected under 35 U.S.C. § 103 as being unpatentable over Markussen et al. (U.S. Patent No. 4,916,212) or Markussen et al. (EPO 163,529) either in view of Goeddel et al. (EPO 055,945), Grau (U.S. Patent No. 4,801,684) and Grau (U.S. Patent No. 4,639,332).

Both Markussen et al. references, Goeddel et al., and both Grau references are applied as above.

It would have been obvious to produce the miniproinsulin precursor taught by Markussen et al. as a fusion protein in a prokaryote as taught by Goeddel et al. It would have been obvious to cleave the fusion protein with cyanogen bromide which would have been a well known cleavage reagent for fusion proteins to one of ordinary skill in the art. It would have been further obvious to treat the resulting miniproinsulin with trypsin as taught by Grau ('332 and '684) to produce a Mono-Arg insulin. One would have been motivated to produce a stable intermediate of insulin for further treatment with carboxypeptidase B to produce insulin for treating diabetes.

Applicant states in the amendment after final rejection that they will overcome Balschmidt et al. based upon their priority document. A certified translation of the document has not been received; however, Balschmidt et al. has been replaced in the grounds of rejection by other teachings disclosing treatment of insulin precursors with trypsin. These references have filing dates prior to the instant priority document.

Applicant argues in the amendment after final rejection that a prima facie case of obviousness has not been made for the compound of claim 1 over Markussen et al. This is not agreed with as Markussen contemplates this precursor in the scope of the claimed and preferred embodiments. Applicant argues that the art rejections over the dependent claims are not proper in view of

their position of no prima facie case being made because all of the art rejections rely upon the Markussen precursor. The Examiner maintains that a prima facie case has been made and applicant has not successfully rebutted the obviousness rejections set forth.

In the amendment after final rejection applicant simultaneously argues that because a prima facie case of obviousness has not been made they are not required to show unexpected results as well as argues unexpected results for the claimed miniproinsulin. The response states that the applicant has informed the attorney of record that many of the embodiments of Markussen et al. do no work according to the claimed processes. (See page 9 of response.) This argument of unexpected results has not been supported by any evidence. There is no evidence of record to show that the embodiments of Markussen et al. could not be used in the methods as claimed or that the miniproinsulin claimed is unexpectedly better in any way.

It is noted with respect to the stated advantages of the claimed miniproinsulin in a "one-pot" reaction in the amendment after final rejection that the specification does not exemplify a method for the preparation of insulin by cleaving the miniproinsulin (formula I) of claim 1 with trypsin to form mono-Arg insulin and cleaving the resulting mono-Arg insulin (formula II) with carboxypeptidase B where these two steps are carried out in

one vessel without having to isolate mono-Arg insulin. (See claim 13.) In example 4, the fusion protein intermediate is isolated and then mono-Arg insulin is formed by using trypsin. The mono-Arg insulin is isolated. (See pages 15 and 16.) Mono-Arg insulin is treated with carboxypeptidase B to form insulin which is then isolated. Neither the reactions nor the isolation of insulin occur in one vessel and isolation of mono-Arg insulin is required. In example 8, miniproinsulin (formula I) is purified from the fermentation supernatant. The intermediate is treated with trypsin and mono-Arg insulin is formed and isolated. (See page 21.) In example 9, mono-Arg insulin is treated with carboxypeptidase B to form insulin which is then isolated. (See page 22.) Neither the reactions nor the isolation of insulin occur in one vessel and isolation of mono-Arg insulin is required. While the specification generally states that the trypsin and carboxypeptidase can be administered simultaneously, this has not been demonstrated nor shown to produce better results than a two-pot reaction or a one-pot reaction with the embodiments of Markussen et al. (See page 5 of specification.)

Claims 6-9 and 14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 and dependent claims 8-9 are confusing in reciting

"compounds" which imply that formula I represents more than one compound. It appears that formula I represents a single compound rather than several compounds. It is noted that claim 1 does not encompass a fusion protein.

Claim 6 is also confusing because it also implies that formula I represents more than one compound in reciting "if the gene structure encodes for a fusion protein." It appears that formula I represents a single compound rather than several compounds.

Claim 14 is confusing in reciting "expressing a DNA molecule encoding the compound of formula I" and "when said compound of formula I is in the form of a fusion protein." These phrases are inconsistent. Formula I of claim 1 is not a fusion protein. A DNA molecule encoding the compound of formula I would not encode a fusion protein.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4227.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen whose telephone number is (703) 308-0666.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Marianne P. Allen

Marianne Porta Allen
Patent Examiner
Art Unit 1812

mpa
October 26, 1993